**INBORN ERRORS OF METABOLISM - I**

# GENETIC TESTING IN INBORN ERRORS OF METABOLISM

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**Abstract**: *Inherited metabolic disorders are a diverse group of genetic disorders that result from disrupted metabolic pathways in the body. Early identification of these disorders is of foremost importance to provide appropriate treatment in time to prevent progression of the disease. Genetic testing panels which include, targeted gene panels, whole exome sequencing and whole genome sequencing help in identifying both pathogenic or likely pathogenic variants, to make a precise molecular diagnosis. A comprehensive combination of clinical and preliminary biochemical evaluations and genetic testing enhances diagnostic accuracy and guides specific interventions. Further, confirming the genetic condition facilitates family screening and genetic counselling. This article highlights the impact of genetic testing on making a definitive diagnosis and helps in managing inherited metabolic disorders.*

**Keywords:** *Metabolic disorder, Genetic testing, Whole exome sequencing, Whole genome sequencing, Genetic counselling*

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## Points to Remember

- ***Inherited metabolic disorders are primarily monogenic conditions, most of which follow an autosomal recessive inheritance pattern.***
- ***Genetic testing plays a crucial role in confirmation of diagnosis, and helps in understanding the disease progression as well as in guiding specific therapies.***
- ***A solid understanding of the genetic mechanisms is essential for selecting the appropriate tests in individual conditions since, several tests are available for diagnosis including Sanger sequencing, next generation sequencing (gene panels, WES, WGS) and MLPA.***
- ***Variants identified in genetic testing are classified into five categories: Pathogenic, likely pathogenic, benign, likely benign and variant of unknown significance. Accurate interpretation of these results requires correlation with the patient's clinical phenotype and metabolic findings.***
- ***Genetic counselling is essential before and after testing. It helps in predicting recurrence risk and facilitates family screening.***

## References

1. Shchelochkov OA, Venditti C P. An approach to inborn errors of metabolism. In: Kliegman RM, St. Geme JW, Blum NJ, Shah SS, Tasker RC, Wilson KM, editors. Nelson Textbook of Pediatrics. 22nd ed. Philadelphia (PA): Elsevier, 2024; pp 803-806.
2. Gospe SM Jr. Pyridoxine-dependent epilepsy - ALDH7A1 [Internet]. In: Adam MP, Feldman J, Mirzaa GM, et al. editors. Gene Reviews®. Seattle (WA): University of Washington, Seattle; 1993-2025 [updated 2022 Sep 22]. Available from: https://www.ncbi.nlm.nih.gov/books.
3. Oder D, Liu D, Hu K, Üçeyler N, Salinger T, Müntze J, et al. α-Galactosidase A genotype N215S induces a specific cardiac variant of Fabry disease. Circ. Cardiovasc. Genet. 2017 Oct; 10(5): e001691.

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4. Eren K, Taktakoðlu N, Pirim I. DNA sequencing methods: from past to present. Eurasian J Med. 2022 Dec; 54(Suppl1):47-56. doi: 10.5152/eurasianjmed. 2022.22280. PMID: 36655445; PMCID: PMC11163357.
5. Huang WJ, Zhang X, Chen WW. Gaucher disease: a lysosomal neurodegenerative disorder. Eur Rev Med Pharmacol Sci. 2015 Apr 1; 19(7):1219-1226.
6. Qin D. Next-generation sequencing and its clinical application. Cancer Biol Med 2019. Feb; 16(1) :4-10. doi: 10.20892/j.issn.2095-3941.2018.0055. PMID: 31119042; PMCID: PMC6528456.
7. Yohe S, Thyagarajan B; Review of clinical next-generation sequencing. Arch Pathol Lab Med.2017 Nov 1; 141 (11): 1544-1557. doi: 10.5858/arpa.2016-0501-RA. Epub 2017 Aug 7. PMID 28782984.
8. Ko A, Youn SE, Kim SH, Lee JS, Kim S, Choi JR, et al. Targeted gene panel and genotype-phenotype correlation in children with developmental and epileptic encephalopathy. Epilepsy Res. 2018;141:48-55. doi:10.1016/j.eplepsyres.2018.02.003.
9. Grody WW, Deignan JL. Diagnostic molecular genetics. In: Rimoin DL, Pyeritz RE, Korf BR, editors. Emery and Rimoin's Principles and Practice of Medical Genetics and Genomics. 7th ed. London: Academic Press; 2020. Chapter 6, p 449 - 453.
10. Stuppia L, Antonucci I, Palka G, Gatta V. Use of the MLPA assay in the molecular diagnosis of gene copy number alterations in human genetic diseases. Int J Mol Sci. 2012;13(3):3245-3276. doi: 10.3390/ijms13033245. Epub 2012 Mar 8. PMID: 22489151; PMCID: PMC3317712.
11. Jahic A, Günther S, Muschol N, Fossøy Stadheim B, Braaten Ø, Kjensli Hyldebrandt H, Kuiper GA, Tylee K, Wijburg FA, Beetz C. "Missing mutations" in MPS I: Identification of two novel copy number variations by an IDUA-specific in house MLPA assay. Mol Genet Genomic Med. 2019 Sep; 7(9):e00615. doi: 10.1002/mgg3.615. Epub 2019 Jul 18. PMID: 31319022; PMCID: PMC6732313.
12. Madry J, Hoffman-Zacharska D, Królicki L, Jakuciñski M, Friedman A. PLP1 gene duplication as a cause of the classic form of Pelizaeus-Merzbacher disease - case report. Neurol Neurochir Pol. 2010 Sep-Oct; 44(5):511-5. doi: 10.1016/s0028-3843(14) 60142-0. PMID: 21082496.
13. Touati G, Mochel F, Rabier D. Diagnostic procedures In: Saudubray JM, Baumgartner MR, Walter J, editors. Inborn Metabolic Diseases: Diagnosis and Treatment. 7th ed. Berlin: Springer; 2022;pp 92-107.
14. He M, Gibson KM. Biochemical studies. In: Hoffmann GF, Nyhan WL, editors. Inherited metabolic diseases: a clinical approach. 2nd ed. Oxford: Oxford University Press; 2017. 2022; pp439-460.
15. Anderson S, Bankier AT, Barrell BG, de Bruijn MH, Coulson AR, Drouin J, et al. Sequence and organization of the human mitochondrial genome. Nature. 1981; 290: 457-65.
16. Mavraki E, Labrum R, Sergeant K, Alston CL, Woodward C, Smith C, et al. Genetic testing for mitochondrial disease: the United Kingdom best practice guidelines. Eur. J. Hum. Genet. 2023 Feb 1; 31(2):148-63.
17. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med 2015 May; 17(5):405-424. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5. PMID:25741868; PMCID: PMC4544753.